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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/596,348

07/14/2006

Thomas Ivo Cremers

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02/20/2009

LUNDBECK RESEARCH USA, INC.

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EXAMINER

RAO, SAVITHA M

ART UNIT

PAPER NUMBER

1614

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/596,348	CREMERS ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on 11 December 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-44 is/are pending in the application.
- 4a) Of the above claim(s) 2-11 and 18-44 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 12-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>07/21/2006, 08/11/2006, 09/18/2007, 04/10/2008</u> .          | 6) <input type="checkbox"/> Other: _____                          |



### **DETAILED ACTION**

Claims 1-44 are pending.

Claims 2-11 and 18-44 are withdrawn from consideration as being drawn towards a nonelected invention.

Claims 1 and 12-17 are under consideration in the instant office action.

### ***Election/Restrictions***

Applicant's election with traverse of Group I (claims 1 and 12-17) in the reply filed on 12/11/2008 is acknowledged. The traversal is on the ground(s) that the office has failed to meet its burden of establishing that the claims and species of compounds of the present invention lack a common special technical feature over the prior art.

Examiner finds the applicant's argument unpersuasive and maintains the restriction since as the Groups are patentably distinct and independent since they lack unity as set forth in the restriction requirement dated 09/18/2008. The subject matter clearly lacks unity of invention for the reasons given in the restriction requirement which is that there is no unifying special technical feature among the different groups thus, the claims are directed to patentably distinct inventions and, thus, do not constitute overlapping subject matter that would result in a coextensive search.

Applicant's election of citalopram as the first compound and thioperamide as the H3-receptor antagonist is acknowledged.

Restriction for examination purposes as indicated is proper. Thereby the restriction requirement is still deemed proper and is therefore made FINAL.

Claims 2-11 and 18-44 are withdrawn from consideration as being drawn towards a nonelected invention

Claims under consideration in the current office action are claims 1 and 12-17.

Applicant timely traversed the restriction (election) requirement in the reply filed on 12/11/2008.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefson et al (EP 0966967, referenced in the instant IDS) in view of Morisset et al (The Journal of Pharmacology and Experimental therapeutics, Vol 288 (2), 1999, 590-596, referenced in the instant IDS), Leurs et al (TIPS, May 1998, Vol (19) 177-183 and Schlicker et al (European Neuropsychopharmacology, Vol 10, supplement 3, Sept 2000, pages 199-200)

Tollefson et al teaches methods and compositions for the treatment of Bipolar disorder, Bipolar depression or unipolar depression by employing a compound having an atypical antipsychotic effect and a serotonin reuptake inhibitor (abstract). The first compound is an atypical antipsychotic such as clozapine, olanzapine, which are both known compounds that are clinically effective in the treatment of schizophrenia [0011] and the second component is a serotonin reuptake inhibitor which among others include citalopram, which drug Tollefson teaches as a serotonin reuptake inhibitor and is clinically effective in depression ([0012], line 40-43). Tollefson teaches the combination of olanzapine/citalopram among the preferred combination [0018]. Tollefson teaches that the adjunctive combination may be administered as a single pharmaceutical compositions which may take any physical form which is pharmaceutically acceptable

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such as tablets [0038] and the inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional [0039] for example capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in the capsules [0040] which reads on the pharmaceutically acceptable carrier limitation of instant claim 12.

Tollefson does not teach clozapine and olanzapine to have H3 receptor antagonistic properties.

However, Morisset et al teaches that clozapine and olanzapine behaves as weak H3 receptor antagonists in vitro with  $K_i$  around 1 and 50  $\mu\text{M}$  respectively. Morisset teaches that despite the modest affinities displayed by both these compounds, the compounds nearly doubled steady-state tele-methyl histamine (t-MEHA) levels in brains with ED50 values comparable to those of potent H3-receptor antagonists (abstract). Morisset teaches that clozapine administration resulted in an enhancement of t-MEHA levels of about 100% i.e. in the same range as that elicited by H3-receptor antagonists such as thioperamide or ciproxifan (page 593, right col. 2nd paragraph).

Leurs teaches that therapeutic potential of histamine H3 receptor agonists and antagonists (title). Leurs teaches that in the mammalian brain, histamine-containing cell bodies are located in the tuberomammillary nucleus of the posterior hypothalamus and project to most cerebral areas indicating that H3 receptor ligands can potentially affect a variety of brain functions. Additionally H3 receptors are involved in the presynaptic regulation of the release of neurotransmitters such as acetylcholine, dopamine, 5-hydroxytryptamine (5-HT) etc. (page 177, left col. 1<sup>st</sup> paragraph to right col. 1<sup>st</sup>

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paragraph). Leurs teaches thioperamide as a prototypic H<sub>3</sub> receptor antagonist which possesses nanomolar affinity for the H<sub>3</sub> receptor and fairly good penetration into the brain. (page 178, left col. 2<sup>nd</sup> paragraph -right col. 1st paragraph). Leurs concludes that the CNS effects of the H<sub>3</sub> receptor antagonists make them interesting candidates for testing in several disorders of the CNS and the highly localized CNS distribution of the H<sub>3</sub> receptor suggests that limited peripheral side-effects will be seen after treatment with an H<sub>3</sub> receptor antagonist (page 182, right col. 3rd paragraph to page 183, left col. 1st paragraph).

Schlicker et al that histamine H<sub>3</sub> receptor is a typical example of a presynaptic autoreceptor in that it is located presynaptically on the nerve endings of the histaminergic neurons in the CNS where its activation produces inhibition of histamine release. It is also located presynaptically on axon terminals of non-histaminergic neurons and thereby H<sub>3</sub>-receptor activation inhibits the release of serotonin, dopamine and noradrenalin in the CNS. (page S199, right col. S.24.02 column1). Schlicker additionally suggests that the blockade of H<sub>3</sub> receptors is an accidental property of already available drugs such as clozapine which is a moderately potent H-3 receptor antagonist (pKi 6.2) (page S200, left col. 2<sup>nd</sup> paragraph)

In view of the foregoing references, the instantly claimed pharmaceutical composition comprising one compound which is a serotonin reuptake inhibitor and a second compound which is a H<sub>3</sub> receptor antagonist having an affinity for the H<sub>3</sub> receptor below 0.5  $\mu$ M would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Tollefson teaches pharmaceutical

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compositions comprising citalopram a serotonin reuptake inhibitor with clozapine and olanzapine. Morisset teaches clozapine and olanzapine to have weak H3 receptor antagonistic activity around 1-50  $\mu\text{M}$ . Leers teaches thioperamide as a prototypic H3-receptor antagonist with nanomolar affinity for the H3 receptors and states that H3 receptors are involved in the presynaptic regulation of the release of neurotransmitters which include 5-HT (serotonin). Schlicker also teaches that H-3 receptor activation inhibits the release of serotonin, dopamine and noradrenalin in the CNS. As such the resulting action of both the H3-receptor antagonists and serotonin reuptake inhibitors (which inhibits the reuptake of serotonin into the presynaptic cells) would be to increase extracellular level of the neurotransmitter serotonin. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. In re Crockett, 126 U.S.P.Q. 186, 188 (CCPA 1960). Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed supra). The natural presumption that two individually known drugs which increases extracellular levels of serotonin and thereby help in treatment of depression would, when combined, provide a third composition also useful for treating depression flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (e.g. unexpected results) to rebut this natural presumption. Accordingly, an ordinarily

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skilled artisan would be motivated to combine the teachings of Tollefson, Morisset, Leurs and Schlicker to develop a composition comprising citalopram and thioperamide.

Since Tollefson has already demonstrated that a serotonin reuptake inhibitor such as citalopram can be combined in a composition with a weak H3 receptor antagonist such as clozapine for treating depression, Leurs provides additional motivation for one of ordinary skill in the art to utilize a stronger H3-receptor inhibitor such as thioperamide instead of clozapine/olanzapine in combination with citalopram in the composition of Tollefson specially for treatment of CNS disorders since there is an highly localized CNS distribution of H3-receptors which would suggest that limited peripheral side effects will be seen after treatment with and H3-receptor antagonist.. Accordingly an ordinarily skilled artisan will be imbued with at least a reasonable expectation of success that such a composition would provide good therapeutic results with decreased side effects.

### ***Conclusion***

Claims 1 and 12-17 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/  
Examiner, Art Unit 1614

/Ardin Marschel/  
Supervisory Patent Examiner, Art Unit 1614